$$a\,\mathfrak{D}\,du^2 + 2a\,(\mathrm{H}-\mathrm{K})\,du\,dv + \mathfrak{D}\,dv^2 = 0 \qquad (15)$$

and defines the pair of lines through y which separate harmonically both the pair of anti-ray tangents and the pair of associate conjugate tangents of the point y.

The two Jacobians (14) and (15) coincide if and only if

$$\frac{\partial^2}{\partial u\,\partial v}\log a = 0, \qquad (3\ bis)$$

i.e., if and only if the original conjugate net is isothermally conjugate. We may state our result as follows:

A necessary and sufficient condition that a conjugate net of curves on a surface be isothermally conjugate is that at each point of the surface the pair of axis tangents, the pair of associate conjugate tangents, and the pair of anti-ray tangents be pairs of the same involution.

By means of the various nets of curves defined in the course of the above interpretation, we have been enabled to deduce a number of properties of isothermally conjugate nets. We have included this more extended discussion in a longer paper, which is a sequel to the one on conjugate nets to which reference has already been made.

[1] L. Bianchi, *Vorlesungen über Differentialgeometrie*, tr. M. Lukat, 2te Aufl., pp. 135 et seq.

[2] E. J. Wilczynski, *Trans. Amer. Math. Soc.*, **16**, 311–327 (1915).

[3] G. M. Green, *Amer. J. Math.*, **37**, 215–246 (1915). Cf. §1.

[4] Ibid., end of §3.

THE RÔLE OF THE LIVER IN ACUTE POLYCYTHAEMIA: THE MECHANISM CONTROLLING THE RED CORPUSCLE CONTENT OF THE BLOOD

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It is very generally considered by all except those who have paid special attention to the subject, that the number of red corpuscles per unit volume of blood is, in the normal individual, a fairly fixed quantity subject to gradual change only. A more careful study shows however that this number is subject to very rapid and great changes, and instead of being constant, that it is continually changing under physiological conditions.

Questions naturally arise as to what factors will cause a change in

the number of red cells;[1] where these changes take place; whether the increase in number is relative or absolute; and finally if there is a mechanism controlling the red corpuscle content of the blood, and if so what is its function.

It has been found that asphyxia in any form causes the number of red cells to increase. Reduced atmospheric pressure, reduced partial tension of oxygen, obstruction of the air passages, reduced oxygen capacity of the blood, as in carbon monoxide poisoning, or increased oxygen consumption as in exercise, will cause an increase in the number of red cells. Furthermore, obstruction to the circulation in the lungs, and consequent interference with the oxygenation of the blood, as in congenital heart conditions, will cause polycythaemia. I have been able to produce this form of polycythaemia experimentally by the injection of either corpuscles hardened with formaldehyde, or an inert powder as lycopodium, or oil, thus inducing embolism of the lungs and obtaining as great an increase in the number of red corpuscles as 3,000,000 in fifteen minutes.

Besides, it is known that various substances occuring physiologically in the body as epinephrin, pituitrin, carbon dioxide, and substances entirely foreign to the body as nicotine, radium chloride, etc., may produce very marked changes in the red count.

And finally I have been able to show that the number of red cells is under nervous control. In cats frightened by a dog for a minute or so, the red count rose one or two millions in five minutes or less, and from excitement alone reached the extreme value of 16,776,000 in one instance and 14,464,000 and 14,920,000 in two other cases.

There has been a great deal of work done concerning the magnitude of the changes in number of red cells and the haemoglobin content of the blood at high altitudes, and in exercise, but up to this time there has been no experimental evidence as to the seat of the changes which cause this increase. On this account the following experiments were systematically undertaken to find out if possible where the changes take place which cause an increase in the number of red cells.

For this purpose epinephrin was chosen as a means of producing polycythaemia, as it can be obtained in a pure state, accurately graduated in amount, and applied as a stimulus with certainty when intravenously injected. Furthermore it occurs normally in the body, and ether does not interfere with its action. When injected in doses of 0.9 mg. per kilo, intravenously, it produces with great regularity an increase of one or two millions in the red count in fifteen or twenty minutes.

To obtain uniform results the animals were etherized, and blood taken from either the jugular or femoral veins by means of a hypodermic needle, which method has been shown to give a true index of the red count in the generally circulating blood.

The entire intestine, its mesentery, the omentum, spleen and pancreas were removed singly, and in other cases altogether, after which epinephrin was injected. Epinephrin caused the same increase in number of red cells in these animals in which the above organs had been removed as in normal animals. It is apparent then that these organs are not the chief seat of the changes by which the red count is increased.

As the liver could not be removed except by the introduction of mechanical complications, its part in the production of polycythaemia was sought by other means.

In the first place animals were completely tied in two above the diaphragm. This is accomplished by opening the chest on both sides between two of the lower ribs, cutting the tissues to the sternum and back bone, and tying the great vessels, the sternum, back bone and adjoining tissues securely with strong ligatures. Except for what blood could pass up and down inside the vertebrae, the animal was completely tied in two above the diaphragm.

In such an animal, the injection of epinephrin caused no increase in the number of red cells.

An operation in which the animal was again tied in two, but this time placing the ligatures about the aorta just below the mesenteric artery and above the renal arteries, and completely tying the rest of the vessels and tissues at this level, gives an animal similar to the one above, except that the blood supply to the liver, spleen, intestine, mesentery, pancreas and omentum has been added. As we know that removal of all these organs except the liver, has no effect on the production of polycythaemia after the injection of epinephrin, we have for our purposes, in this case merely added the liver to the animal which was divided above the diaphragm.

Epinephrin injected into such an animal increases the number of red cells as in a normal animal.

From these experiments it appears that the liver is the seat of the changes which cause an increase in number of red cells. Further proof of this was obtained by quite different means.

On account of the irregularity with which the hepatic artery branches it was considered a more certain means of shutting off the arterial blood supply to the liver to ligate the coeliac axis artery, than to attempt ligation of the hepatic artery. The coeliac axis artery supplies the

liver, spleen and pancreas, and part of the stomach, but we have seen that removal of all of these except the liver has no effect on the production of polycythaemia after injection of epinephrin. If then the coeliac axis artery is ligated, and epinephrin injected, no change in the number of red cells is observed, but if this ligature is removed, even one-half hour after the injection of epinephrin, the red count will immediately increase, as if the usual dose of epinephrin had been injected into a normal animal.

A control experiment was done in which the coeliac axis artery was ligated, and after half an hour the ligature removed. This had no effect on the red count, which shows that mere interruption of the arterial circulation to the liver is not the only factor necessary to change the number of red cells.

I have also shown that ligation of the portal vein, as in the operation of removing the intestine, has no effect on the production of polycythaemia following the injection of epinephrin. Also in those cases in which the hepatic artery was ligated, epinephrin was carried to the liver by the uninterrupted portal circulation, and yet no change in the number of red cells took place.

Furthermore, in cases where the hepatic artery was tied, injection of epinephrin caused no increase in the number of red cells, although there was no interference with the blood supply to the kidneys, bone marrow, muscles, lungs or skin. These organs may then be considered as playing no part in the production of polycythaemia due to epinephrin injection.

It appears then that the liver is the organ capable of increasing the red corpuscle content of the blood after injection of epinephrin, and that the arterial blood supply to the liver must be intact to allow these changes to take place.

As to the changes which occur in the liver certain facts were observed in these experiments. There is a decrease in plasma volume, not however sufficient to account entirely for the increase in number of red cells. There are cells present in the circulation during polycythaemia which were not there before its production, as shown by a decrease in the average size of the red corpuscles, and a decrease in their percentage haemoglobin content. These cells show none of the usual signs of young cells. That is, they are not nucleated, they show no change in fragility, and they have no increased metabolism such as would result in an increased rate of reduction.

Concerning the mechanism which normally controls the red count, a few points of interest were observed.

It has been found that the red count is under nervous control, as shown by the increase in the number of red corpuscles after stimulation of the vago-sympathetic trunks, after asphyxia of the brain alone, and after emotional excitement as fear, rage, etc. It was also shown that the adrenals play a part in this mechanism, as epinephrin has been proved to be one of the most powerful means of increasing the number of red cells, and as the chief physiological stimuli which produce polycythaemia, namely asphyxia, exercise, fear, rage, etc., all cause a reflex stimulation of the adrenals, and an increased epinephrin output. Removal of the adrenals was found to exclude the production of polycythaemia in asphyxia, fear and rage, and after the injection of pituitrin, although these same animals responded to the injection of epinephrin by the usual increase in number of red cells. Furthermore, removal of the adrenals is followed after several hours by a complete loss of control of the red count.

When the number of red cells is increased in acute polycythaemia, we have seen that there is also an increase in haemoglobin, but not in proportion to the increase in number of red cells. This being the case, the blood is better equipped not only to carry more oxygen, but on account of the increased surface of the haemoglobin, to take up more oxygen per unit of time. The body is then better prepared to maintain a constant oxygen content of the blood under various physiological and pathological conditions.

We may therefore conclude that there is in the body a mechanism for regulating the red corpuscle content of the blood; that this mechanism is under nervous control, responding to nervous, chemical and emotional stimuli; that the adrenal glands play a part in this mechanism, and that the liver is the seat of the changes which increase the number of red cells, partly by a reduction in plasma volume, and partly by bringing cells into the circulation which are not normally present.[2]

[1] The terms red count, number of red cells, etc., will be used for the sake of brevity instead of the more exact phrase "Number of red corpuscles per unit volume of blood."

[2] This article is given in full in the *Journal of Pharmacology and Experimental Therapeutics*, Vol. 7, Nos. 1 and 2 (1915).